many) M-MLV Reverse Transcriptase according to the manufacturer's instructions. The amplification of V_H and V_L genes was carried out in a 25 µl volume with 1.75 mM $MgCl_2$, 0.4 pM primer, 200 µM of each dNTP, and 1U Taq polymerase (MBI Fermentas, St. Leon-Rot, Germany). The PCR-products were amplified using the following cycle profiles: 95°C for 2 min, followed by 35 cycles of 94°C for 30 sec; 65°C for 30 sec (for VH3 and VH4 primers), 60°C for VH1, VH2, VH5, VH6 and 52°C for VL primers respectively; a final extension at 72°C for 4 min.

Sequencing the Antibody

The PCR products were purified using gel electrophoresis through 2% agarose (Roth, Karlsruhe, Germany) followed by gel extraction of the PCR product using a Jetsorb gel extraction kit (Genomed, Bad Oeynhausen, Germany). The PCR products were then cloned using the pCR-Script Amp SK^+ cloning kit (Stratagene, Heidelberg, Germany). Ten positive clones were sequenced using the DyeDeoxy termination cycle sequencing kit (Applied BioSystems Inc., Weiterstadt, Germany) and analysed with an ABIPrism373 automated DNA sequencer (both strands were sequenced using T3 and T7 primers). The sequences were analysed using the DNASIS for Windows sequence comparison software and the GenBank and IMGT/V-QUEST databases. The International Immunogenetics ("IMGT") database is coordinated by Marie-Paule Lefranc at the Université Montpellier, Montpellier, France.

Immunhistochemical staining of paraffin sections

Paraffin-embedded human tissues were sectioned (2µm), the paraffin was removed as follows:

Deparaffinisation:

- Xylene 1 5 min
- Xylene 2 5 min
- 100% Ethanol 1 5 min
- 100% Ethanol 2 5 min
- Methanol (70ml) + H_2O_2 (500µl) 5 min
- 90% Ethanol 1 3 min
- 90% Ethanol 2 3 min
- 80% Ethanol 1 3 min
- 80% Ethanol 2 3min
- 70% Ethanol 1 3 min
- 70% Ethanol 2 3 min
- wash once with Tris/NaCl
- cook: 300 ml dest. H_2O in a pressure cooker
  add Citric acid into the inset and cook for 5 min
- block 15 min with BSA/PBS, 150µl per microscope slides
- wash once with Tris/NaCl
- first antibody: 150µl per microscope slides ,incubate for 2,5h in a humidified chamber. at 37°C ,
- wash three times with Tris/NaCl
- second antibody: 150µl per microscope slides, incubate for 45 min in a humidified chamber at room temperature (700µl PBS + 300µl AB-Plasma + 20µl antibody)
- wash three times with Tris/NaCl
- put for 10 min in PBS
- incubate 10 min with diaminobenzidine(0.05%) –hydrogen peroxide (0.02%): 150µl per microscope slides
- wash three times with H_2O , then wash once with dest. H_2O
- put for 5 min into hematoxylin
- put 10-15 min under running tap water

- wash with dest. H_2O
- cover with glycerol gelatine

Preparation of tumor cell membrane extracts

Isolation of membrane proteins from tumor cells was performed as described using standard methods in the art, as described, for example, in Hensel et al. (Int. J. Cancer 81:229-235, 1999). In particular, confluent tumor cells (BXPC-3 and 23132/87) were washed twice with PBS, harvested with a cell scraper, centrifuged, and resuspended in hypotonic buffer (20mM HEPES, 3mM KCl, 3mM $MgCl_2$) and incubated for 15 minutes on ice. The cells were then sonicated for 5 minutes and the nuclei were pelleted by centrifugation at 10,000 x g for 10 min. The supernatant was centrifuged for 40 minutes at 100,000 x g in a swing-out rotor to pellet the membranes. After washing the pellet with hypotonic buffer, the pellet was resuspended in membrane lysis buffer (50 mM HEPES pH 7.4, 0.1 mM EDTA, 10% glycerol, and 1% Triton X-100). Complete protease inhibitor (Boehringer, Mannheim, Germany) also was added to all solutions.

Western blotting

Western blots were preformed using standard techniques as described, for example, in Hensel et al. (Int. J. Cancer 81:229-235, 1999). In short, blotted nitrocellulose membranes were blocked with PBS containing 3% low fat milk powder, followed by incubation for 1 hour with 20-40µg of SAM-6 human IgM antibodies or unrelated human control IgM (ChromPure IgM, Dianova). The secondary antibody (peroxidase-coupled rabbit anti-human IgM antibody 1:1,000, Dianova) was detected with the SUPERSIGNAL chemiluminescence kit from Pierce (KMF, St. Augustin, Germany).

Ultra-structural studies

Adherent growing stomach carcinoma cell line 23132/87 was incubated with 10µg/ml SAM-6 antibody or unrelated human control IgM for the indicated periods of time. Then the slides were fixed with 2,5% glutaraldehyde (electron microscopy) or 6,25% glutaraldehyde in Soerensen buffer pH 7,4 (for raster electron microscopy) and prepared for microscopical analysis. Morphology of cells was investigated with scanning electron microscopy and transmission electron microscopy.

Sudan III staining

For intracellular lipid staining stomach carcinoma cells 23132/87 were grown on glass slides. Adherent cells were incubated for 48 h with antibody SAM-6 (30µg/ml). After two washing steps with PBS cells were fixed for 5 min with 60% isopropanol. Before use, a 60% solution of the Sudan III stock (0,5% Sudan III in 100% isopropanol) was matured overnight, filtered and added to the fixed cells. After 15 min cells were washed with distilled H2O, differentiated in 60% isopropanol, washed again and then counterstained for 6 min with Mayers Hemalaun. Finally cells were rinsed with water for 10 min, washed with distilled H2O and mounted with glycerol gelatin.

Nile red staining

The neutral lipid staining with the phenoxazine dye Nile red was performed as described before (Greenspan, P., Mayer, E.P., and Fowler, D. Nile Red: A Selective Fluorescent Stain for Intracellular Lipid Droplets. J. Cell Biol. *100*, 965-973, 1985). Briefly, stomach carcinoma cells 23132/87 were grown on glass plates and adherent cells were incubated with SAM-6 antibody (30g/ml) for 48 h. Cells were then fixed with 1,5% glutaraldehyde for 5 min, washed with

HEPES buffer and incubated in a 1:200 dilution of Nile Red in HEPES buffer (stock solution 1mg/ml Nile red in aceton). After an additional washing step with HEPES buffer cell nuclei were stained with DAPI (dilution 1:1000 in water) for 8 min. Cells were then washed again and mounted with Fluoromount-G (SOUTHERN Biotechnology Ass., Inc., USA). Fluorescence analysis was performed with Leica TCS SP2 confocal laser microscope. Polar lipids are stained dark red (543 nm), neutral lipids are stained yellow (488 nm) and cell nuclei appear blue (350 nm).

Detection of oxLDL

LDL (Sigma, Taufkirchen, Germany) was oxidised by incubation with 20µM $CuSO_4$ for 3 respectively 15h . The amount of oxidiesed LDL was determined with the Mercodia Oxidised LDL ELISA(Mercodia, Uppsala, Sweden)

Mercodia Oxidised LDL ELISA is a solid phase two-site enzyme immunoassay. It is based on the direct sandwich technique in which two monoclonal antibodies are directed against seperate antigenic determinants on the oxidised apolipoprotein B molecule. During incubation oxidised LDL in the sample reacts with anti-oxidiesed LDL antibodies bound to microtitration well. After washing, that removes non-reactive plasma components, a peroxidase conjugated anti-human apolipoprotein B antibody recognizes the oxidiesed LDL bound to the solid phase. After a second incubation and a single washing Stepp that removes unbound enzyme labeled antibody, the bound conjugate is detected by reaction with 3, 3´, 5, 5´-Tetramethylbenzidin (TMB). The reaction is stopped by adding acid to give a colorimetric endpoint that is read spectrophotometrically at 450nm.

Measuring the SAM-6 – oxLDL interaction

Flexible, flat bottom 96-well plates (Becton Dickinson Labware Europe, France) were incubated with the different oxidised LDL over night at 4°C. Then the plates were blocked using RPMI-1640 medium containing 10% FCS for one hour. Subsequently the plates were incubated with 60µg/ml SAM-6 antibody diluted in PBS for one hour at 37°C. After washing with PBS three times the plates were incubated with HRP-coupled secondary antibody (rabbit anti human IgM, Dako, Hamburg, Germany) diluted 1:1000 in PBS. Then the plates were washed once with PBS and twice with citrat buffer followed by incubation with OPD (DakoCytomation, Glostrup, Denmark) and measurement at 490nm in an ELISA-reader.

Chromatographic analysis of intracellularly enriched lipids

BXPC-3 cells were incubated with 30µg SAM-6 antibody respectively human unrelated control IgM (Chrompure IgM, Dianova, Germany) for 24h. Then the cells were detached using trypsin/EDTA, followed by two washing Stepps with PBS. The cell pellets were stored at –20°C until usage. Lipids were extracted from the cell pellets. The extracted lipids were disolved in 250µl Chloroform/Methanol (2:1) and 10 respectively 25µl were spread at the starting point of a thin layer chromatography plate (coated with SiO_2, silica gel). At the outer right and left side the markers with different known lipids (cholesterolester, cholesterol, triglycerids, oleic acid, phospatidylethanolamine, phosphatidylcholine, sphingomyeline) were loaded.

For unpolar lipids hexan/ethylacetat/ acetic acid (90/10/1) was used as organic solvent, for phospholipids etc. chloroform/methanol/H_2O (70/30/5) was used. The staining was prepared using a „Kägi-Miescher" aerosloic reagent (anisaldehyde/sulphuric acid solved in

acetic acid) followed by heating to 150°C until the staining was optimal.

Detection of SAM-6 activity *in-vivo*

To determine the effects of antibody SAM-6 on tumor cell growth *in vivo*, a *scid*- mouse/human pancreas carcinoma cell system was used. C.B-17/IcrHanHsd-*scid* mice (Harlan Winkelmann GmbH, Borchen, Germany) (age 6-8 weeks, n=10 per group) were inoculated with 2 x 10^6 human pancreas carcinoma cells (cell line BXPC-3) at day 0 subcutaniously, followed by injections of SAM-6 antibody (200 µg) at days 1, 3, 5, 7 and 9 i.p. post carcinoma cell injection. Control mice were injected with unrelated human IgM (Chrompure IgM, Dianova, Hamburg, Germany) in the same concentration. Visible tumor growth was measured macroscopically during the experiment. The experiments were terminated when tumors had reached maximal tolerable size (day 25), whereupon the mice were sacrificed, tumor volume respectively tumor weight was determined.

Example 2

Generation of the Cell Line Expressing the SAM-6 Monoclonal Antibody

As described above, we obtained the SAM-6 monoclonal antibody expressing hybridoma by fusing lymphocytes obtained from the spleen or lymph nodes of a cancer patient with the heteromyeloma cell line HAB-1 (Faller, et al., Br. J. Cancer 62:595-598, 1990). The lymphoid sources were not pre-selected in terms of the age or sex of the patient. The resultant cell is a type of hybridoma known as a trioma, as it is the fusion of three cells. Like normal B-lymphocytes, this trioma has to ability to produce antibodies. The specificity of the

trioma, as it is the fusion of three cells. Like normal B-lymphocytes, this trioma has to ability to produce antibodies. The specificity of the antibody is determined by the specificity of the original lymphocyte from the patient that was used to generate the trioma.

The hybridoma supernatants were screened for antibody production using an ELISA assay. Following ELISA, antibodies were primarily tested immunohistochemically against their autologous tumor for tumor specific reactivity. The SAM-6 antibody was generated from the stomach of a patient with adenocarcinoma.

The amino acid sequence (SEQ ID NO:1) and the nucleic acid sequence (SEQ ID NO:2) of the variable region of the light chain of human monoclonal antibody SAM-6 are shown in Figure 8a and 8b; the amino acid sequence (SEQ ID NO:3) and the nucleic acid sequence (SEQ ID NO:4) of the variable region of the heavy chain of human monoclonal antibody SAM-6 are shown in Figure 9a and 9b. In 8b and 9b different complementarity- determining regions (CDRs) are indicated. The complementartity-determining regions (CDRs) of the polypeptides sequence comprises a amino acid sequences that are substantially identical to the amino acid sequences Ser-Gly-Asp-Lys-Leu-Gly-Asp-Lys-Tyr-Ala-Cys (CDR1), Gln-Asp-Ser-Lys-Arg-Pro-Ser (CDR2) and Gln-Ala-TrpAsp-Ser-Ser-Ile-Val-Val (CDR3) of SEQ ID NO 1 of the variable region of the light chain (V_L). While the complementarity –determining regions (CDRs) of the polypeptides amino acid sequence comprises a amino acid sequences that are substantially identical to amino acid sequence Ser-Tyr-Ala-Met-His (CDR1), Val-Ile-Ser-Tyr-Asp-Gly-Ser-Asn-Lys-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly (CDR2) and Asp-Arg-Leu-Ala-Val-Ala-Gly-Lys-Thr-Phe-Asp-Tyr (CDR3) of SEQ ID No 3 of the variable region of the light chain (V_H).

Example 3

Immunohistochemical Characterization of an Antibody

To characterize the monoclonal antibody secreted by a hybridoma, we tested the antibody against a panel of normal and tumor tissues using an immunoperoxidase assay as described in the materials and methods. This assay provided us with an overview of which tissues were stained by the antibody and of the distribution of the antigen.

Antibodies that are specific for tumor cells and not for normal tissue were further characterized. First, we tested these antibodies against the same types of tumors from different patients. We then tested these antibodies against tumors of other organs and, finally, against normal tissues. Using these assays, we identified the human SAM-6 monoclonal antibodies. The tumor reactive antibodys generated and described in this study is of the IgM/λ isotype (see Table 1).

Table 1: Origin of Monoclonal IgM Antibodies and Clinical Data of Cancer Patients

Antibody	Organ	Tumor-Type	Tumor-stage	Tumor-grade	Age	Sex	Source Of Lymphocytes	Ig Class
SAM-6	Stom-ach	Adeno-carci-noma	T2N2	G3	51	M	Spleen	IgM/λ

To investigate the genetic origin of this human monoclonal IgM antibodys the V_H and V_L genes were amplified, cloned and sequenced. The sequences were compared with germ-line sequences in the IMGT/V-QUEST database to identify the most homologous germ-line

genes and to detect somatic mutations. The results are represented in Table 2.

Table 2: Characterization of Variable Heavy and Light Chain Regions of Monoclonal IgM Antibodies

	Heavy chain				Light chain			
Antibody	Germ-line Gene	Homology (%)	R/S Frame	R/S CDR	Germ-line gene	Homology (%)	R/S Frame	R/S CDR
SAM-6	IgHV3-30.3*01	100	0/0	0/0	IgLV3-1*01	99,6	1/0	0/0

The high homology (100%) of the VH region to the germ-line gene and the low R/S ratio, which is an indicator for affinity maturation of antibodies, indicates that the antibody did not underwent affinity maturation due to antigen contact. The degree of identity of the nucleotide sequence of the V_L segment to the most homologous V_L germ-line gene is again high. The data indicate that the SAM-6 antibody belongs to the family of naturally occurring, non-affinity matured antibodies.

After initial testing on autologous tumors, the reaction patterns of the antibodies were investigated in greater detail using immunohistochemical staining on a variety of paraffin-embedded carcinomas and normal tissues. The SAM-6 antibody exhibited no binding activity with normal tissues (Table 3).

Table 3: Reaction Pattern of the Monoclonal SAM-6 Antibody an Normal Tissue

Tissue	SAM-6
Esophagus	-
Stomach	-

Colon	-
Pancreas	-
Lung	-
Breast	-
Uterus	-
Thyroid gland	-
Testis	-

In contrast, the SAM-6 antibody shows reactivity with different tumor tissues (table 4).

Table 4: Reaction Pattern of the Monoclonal IgM SAM-6 Antibody on Tumor Tissues

Tissue	Carcinoma Type	Pos	Neg
Esophagus	Squamous cell	3	0
	Adeno (Barrett)	4	0
Stomach	Adeno (diffuse)	4	0
	Adeno (intestinal)	3	0
Colon	Adeno	3	0
Pancreas	Adeno (ductal)	3	0
Lung	Adeno	3	0
	Squamous cell	3	1
Breast	Invasive (ductal)	4	0
	Invasive (lobular)	4	0
Ovary	Adeno	3	0
Uterus	Adeno	4	0
Prostate	Adeno	5	2

The positive reaction of antibody SAM-6 was not restricted to adenocarcinoma of the stomach as clear positive reactions were observed, among others, on invasive lobular carcinoma of the breast (Fig. 1A), adenocarcinoma of the colon (Fig. 1B), and squamous cell carcinoma of the esophagus (Fig. 1C). The positive control antibody used in these experiments was a mouse monoclonal antibody against human cytokeratin 5/6 ("CK 5/6;" Dako A/S, Denmark) or a mouse monoclonal antibody against human cytokeratin ("CAM 5.2;" Becton Dickinson, New Jersey).

To examine the antigen recognized by the antibody, Western blot analysis was performed with membrane extracts of established carcinoma cell lines. The antibody SAM-6 produced one specific band on stomach carcinoma cell line 23132/87 and pancreas adenocarcinoma cell line BXPC-3. Antibody SAM-6 reacted with membrane proteins of about 140 kDa (Fig. 3A). To rule out non-specific binding of IgM antibodies to membrane extracts, unrelated human control IgM was used as control.

Example 4
Determining whether an Antibody Induces Apoptosis

A number of assays standard in the art may be used to determine if an antibody induces apoptosis of a cell.

For example, we used the CELL DEATH DETECTION ELISA^{PLUS} (Roche, Mannheim, Germany) to analyze the extent to which the SAM-6 antibody induces apoptosis. The cell death detection ELISA is based on a quantitative sandwich-enzyme-immunoassay principle using mouse monoclonal antibodies directed against DNA and histones, respectively. This assay allows the specific determination of mono- and oligo-nucleosomes which are released into the cytoplasm of cells which die from apoptosis.

In particular, 1 x 10^4 tumor cells (BXPC-3, 23132/87, RPMI-2650 and HNEpC-c) were plated on 96-well plates and incubated in presence of different concentrations of the human IgM-antibodies for 24 hours at 37°C and 7% CO_2 in an CO_2 incubator. Depleted cell culture supernatant with unrelated IgM antibodies served as negative control. After the incubation period, the cells were centrifuged for 10

minutes and the supernatants were removed. The resulting cell pellets were then incubated with lysis-buffer for 30 minutes at room temperature. After centrifugation the supernatants were transferred into a streptavidin-coated microtiter plate (MTP) and immunoreagent (a mixture of 10% Anti-Histone-Biotin, 10% Anti-DNA-peroxidase (Anti-DNA POD) and 80% incubation buffer) added before incubation for 2 hours at room temperature on a MTP shaker at 250 rpm. Following the incubation period, unbound components were removed by a washing step with incubation buffer. POD was determined photometrically with ABTS™ as a substrate (1 ABTS™ (2,2'-Azino-di[3-ethyl-benz-thiazolin-sufonat) tablet in 5 ml substrate buffer). Antibody-induced apoptosis was measured by determining the color intensity of the green precipitate that it formed as a result of this reaction using an ELISA reader at a wavelength of 405 nm in comparison to ABTS™ solution as a blank (reference wavelength of approximately 490 nm). Based on this color intensity, we calculated the level of the antibody-induced apoptosis. These experiments clearly showed that SAM-6, induces apoptosis in carcinoma cells after 48 hours of incubation (Fig. 3B).

The Y-axis in this figure is the difference between the absorbance at 415 nm and at the 490 nm reference wavelength (A_{415}-A_{490}) and the negative control is RPMI 1640 medium. The concentration of the SAM-6 antibody was either 4 µg/ml in supernatant.

Example 5

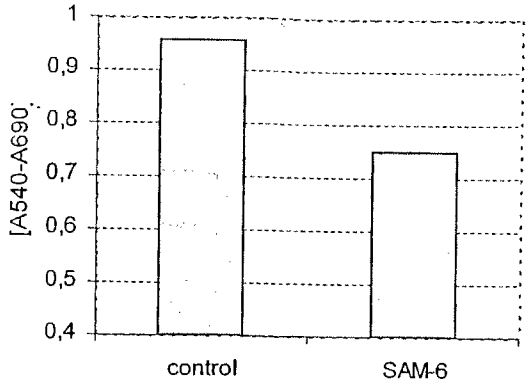
Determining whether an Antibody Inhibits Cell Proliferation

Cell proliferation may be assayed by a number of methods that are standard in the art, for example, by the reduction of tetrazolium salts. The yellow tetrazolium salt 3-(4,5-dimethylthiazol-2-yl) - 2,5-

diphenyltetrazolium bromide ("MTT") (Sigma, St. Louis, MO), is reduced by metabolically active cells, in part by the action of mitochondrial dehydogenase enzymes to generate reducing equivalents such as NADH and NADPH. The resulting intracellular purple formazan can be solubilized and quantified by spectrophotometric means. The MTT cell proliferation assay measures the rate of cell proliferation and, when metabolic events lead to apoptosis, the reduction in cell viability.

For the MTT assay, we trypsinized cells (23132/87) and resuspended the cells in 10 ml of RPMI-1460 medium contains 10% Fetal Calf Serum (FCS), 1% glutamine, and 1% penicillin/streptomycin (complete medium). The cells were then counted and diluted to 1 x 10^6 cells/ml. 50 µl of this suspension were pipetted into wells of a 96-well plate, resulting in approximately 5 x 10^4 cells/well. The first row of wells was left empty. We then added 50 µl of the antibody diluted in complete medium to each well. The 96-well plate was then incubated for 24 hours in a 37°C incubator. After the incubation period, 50 µl MTT solution (5 mg/ml in PBS) were added to each well. The 96-well plate was incubated for 30 minutes at 37°C and centrifuged for 5 minutes at 800 g. The supernatant was aspirated, 150 µl of dimethylsulphoxide (DMSO) were added to each well, and the cell pellet was resuspended. Absorption was determined at a wavelength of 540 nm and at a reference wavelength of 690 nm in an ELISA reader.

After 24 hours, the SAM-6 antibody inhibited cell proliferation of the tumor cell line, while the controls with depleted cell culture supernatant remained unchanged (see the following figure).



MTT Proliferation Assay; Cell line: 23132/87, Control: RPMI-1640, Antibody: SAM-6 (concentration 4µg/ml), Time of incubation: 24h

Example 6

In Vivo Imaging of a Neoplasm

A patient suspected of having a neoplasm, such as a colorectal carcinoma, may be given a dose of radioiodinated SAM-6 antibody, or another tumor-specific polypeptide, and radiolabeled unspecific antibody using the methods described herein. Localization of the tumor for imaging may be effected according to the procedure of Goldenberg et al. (N. Engl. J. Med., 298:1384, 1978). By I.V. an infusion of equal volumes of solutions of ^{131}I- SAM-6 antibody and Tc-99m-labeled unspecific antibody may be administered to a patient. Prior to administration of the reagents I.V., the patient is typically pre-tested for hypersensitivity to the antibody preparation (unlabeled) or to antibody of the same species as the antibody preparation. To block thyroid uptake of ^{131}I, Lugol's solution is administered orally, beginning one or more days before injection of the radioiodinated antibody, at a dose of 5 drops twice or three-times daily. Images of various body regions and views may be taken at 4, 8, and 24 hours after injection of the labeled preparations. If present, the neoplasm, e.g., a colorec-

tal carcinoma, is detected by gamma camera imaging with subtraction of the Tc-99m counts from those of ^{131}I, as described for ^{131}I-labeled anti-CEA antibody and Tc- 99m-labeled human serum albumin by DeLand et al. (Cancer Res. 40:3046, 1980). At 8 hours after injection, imaging is usually clear and improves with time up to the 24 hour scans.

Example 7

Treatment of a Neoplasm Using Labeled Antibody Mixtures

A patient diagnosed with a neoplasm, for example, a female patient diagnosed with a breast carcinoma, may be treated with the polypeptides of the invention as follows. Lugol's solution may be administered, e.g., 7 drops 3 times daily, to the patient. Subsequently, a therapeutic dose of ^{131}I-SAM-6 antibody may be administered to the patient. For example, a ^{131}I dose of 50 mCi may be given weekly for 3 weeks, and then repeated at intervals adjusted on an individual basis, e.g., every three months, until hematological toxicity interrupts the therapy. The exact treatment regimen is generally determined by the attending physician or person supervising the treatment. The radioiodinated antibodies may be administered as slow I.V. infusions in 50 ml of sterile physiological saline. After the third injection dose, a reduction in the size of the primary tumor and metastases may be noted, particularly after the second therapy cycle, or 10 weeks after onset of therapy.

Example 8

Treatment Using Conjugated Antibodies

A patient diagnosed with a neoplasm, for example, a female patient with breast cancer that has metastasized to the chest and lungs, may

be treated with solutions of ^{131}I- SAM-6, ^{10}B- SAM-6 and a Tc-99m labeled unspecific antibody. An amount of ^{131}I-labeled SAM-6 antibody (in 50 ml of sterile physiological saline) sufficient to provide 100 mCi of ^{131}I activity based on a 70 kg patient weight may be administered to the patient. This dosage is equal to 3.3 mg of an antibody having 40-80 Boron atoms and 8-16 Boron-10 atoms per antibody molecule. The neoplasm is first precisely localized using the procedure of Example 6. In addition, Lugol's solution should be continuously administered to the patient, as in the previous example. A well-collimated beam of thermal neutrons may then be focused on the defined tumor locations. Irradiation with an external neutron beam dose of 400-800 rads, delivered in a period of from 8-20 min, is effected for each tumor locus, and is optionally repeated with administration of the tumor-locating antibody, with or without the radiolabel, at intervals adjusted on an individual basis, but usually not exceeding a total dose of 3200 rads unless simultaneous external irradiation therapy is indicated. If desired, in addition to this therapy, an antitumor agent, such as a chemotherapeutic agent, may also be administered to the patient.

Other Embodiments

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth.

We claim:

1. A purified polypeptide that binds to neoplastic cells, wherein said polypeptide has an amino acid sequence substantially identical to the sequence of SEQ ID NO 1 and/or SEQ ID NO 3, and wherein said polypeptide specifically binds to BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU-NH91 (DSMZ Accession No. ACC 393) cells and not to non-neoplastic cells.

2. A purified polypeptide that binds to neoplastic cells, wherein said polypeptide has an amino acid sequence substantially identical to the sequence of SEQ ID NO 1 and/or SEQ ID NO 3, and wherein said polypeptide specifically binds to BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196) and LOU-NH91 (DSMZ Accession No. ACC 393) cells and not to non-neoplastic cells, and wherein said neoplastic cell is a adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, adenocarcinoma of the esophagus lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus cell.

3. A purified polypeptide that binds to neoplastic cells, wherein said polypeptide has an amino acid sequence substantially identical to the sequence of SEQ ID NO 1 and/or SEQ ID NO 3, and wherein said polypeptide specifically binds to a adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus cell and not to a non-neoplastic cell.

4. The purified polypeptide of claim 1, 2 or 3, wherein said polypeptide inhibits cell proliferation when bound to a neoplastic cell, but does not inhibit cell proliferation of a non-neoplastic cell.

5. The purified polypeptide of claim 1, 2 or 3, wherein said polypeptide
   - binds to low density lipoproteins (LDL) and/or oxidised low density lipoproteins (oxLDL), and/or
   - binds to very low density lipoproteins (VLDL), and
   - induces the intracellular accumulation of lipids when bound to a neoplastic cell, but does not induce the intracellular accumulation of lipids in a non-neoplastic cell.

6. The purified polypeptide of claim 1, 2 or 3, wherein said polypeptide induces apoptosis of a neoplastic cell to which it binds, but does not induce apoptosis of a non-neoplastic cell.

7. The purified polypeptide of claim 1, 2 or 3 wherein said polypep-

tide comprises an antibody or a functional fragment thereof.

8. The purified polypeptide of claim 7, wherein said polypeptide is a functional fragment selected from the group consisting of V_L, V_H, F_V, F_C, Fab, Fab', and $F(ab')_2$.

9. The purified polypeptide of claim 8, wherein said polypeptide has an amino acid sequence of the variable region of the light chain (V_L) substantially identical to SEQ ID NO 1 or/and an amino acid sequence of the variable region of the heavy chain (V_H) substantially identical to SEQ ID NO 3.

10. The purified polypeptide of claim 8, wherein said polypeptide has a nucleic acid sequence of the variable region of the light chain (V_L) substantially identical to SEQ ID NO 2 or/and a nucleic amino acid sequence of the variable region of the heavy chain (V_H) substantially identical to SEQ ID NO 4.

11. The purified polypeptide of claim 8, wherein said functional fragment comprises a fragment of the sequence of SEQ ID NO:1 and SEQ ID NO:3.

12. The purified polypeptide of claim 8, wherein said functional fragment comprises a fragment that is substantially identical to the sequence of SEQ ID NO:1 or SEQ ID NO:3.

13. The purified polypeptide of claim 1, 2, or 3, wherein said polypeptide comprises a sequence that is substantially identical to the amino acid sequence of SEQ ID NO:1.

14. The purified polypeptide of claim 1, 2 or 3, wherein said polypeptide comprises a sequence that is substantially identical to the amino acid sequence of SEQ ID NO:3.

15. The purified polypeptide of claim 1, 2 or 3, wherein said polypeptide comprises a nucleic acid sequences that are substantially identical to nucleotides 67-99 (CDR1), 145-165 (CDR2) and 262-288 (CDR3) of SEQ ID NO 2.

16. The purified polypeptide of claim 1, 2, or 3, wherein said polypeptide comprises a nucleic acid sequences that are substantially identical to nucleotides 91-105 (CDR1), 148-198 (CDR2) and 295-330 (CDR3) of SEQ ID NO 4.

17. A purified polypeptide comprising the amino acid sequence of SEQ ID NO:1.

18. A purified polypeptide comprising the amino acid sequence of SEQ ID NO:3.

19. A purified polypeptide comprising the amino acid sequence of SEQ ID NO:1 and/or SEQ ID NO: 3.

20. A purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18 or 19 having at least one complementarity-determining regions (CDR) or functional fragments thereof comprising the amino acid sequence substantially identical to the amino acid sequence Ser-Gly-Asp-Lys-Leu-Gly-Asp-Lys-Tyr-Ala-Cys (CDR1) or Gln-Asp-Ser-Lys-Arg-Pro-Ser (CDR2) or Gln-Ala-Trp-Asp-Ser-Ser-Ile-Val-Val (CDR3) of SEQ ID NO: 1 and/or Ser-Tyr-Ala-Met-His (CDR1) or

Val-Ile-Ser-Tyr-Asp-Gly-Ser-Asn-Lys-Tyr-Tyr-Ala-Asp-Ser-Val-Lys-Gly (CDR2) or Asp-Arg-Leu-Ala-Val-Ala-Gly-Lys-Thr-Phe-Asp-Tyr (CDR3) SEQ ID NO: 3.

21. The purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20, wherein said polypeptide is a monoclonal antibody.

22. The purified polypeptide of claim 21, wherein said monoclonal antibody is a human monoclonal antibody.

23. A cell that expresses the polypeptide of claim 1, 2 or 3.

24. A cell that expresses a polypeptide that comprises a sequence that is substantially identical to the amino acid sequence of SEQ ID NO:1.

25. The cell of claim 24, wherein said polypeptide comprises the sequence of SEQ ID NO:1.

26. A cell that expresses a polypeptide that comprises a sequence that is substantially identical to the amino acid sequence of SEQ ID NO:3.

27. The cell of claim 26, wherein said polypeptide comprises the sequence of SEQ ID NO:3.

28. A cell that expresses a polypeptide that comprises the amino acid sequence of SEQ ID NOS:1 and 3.

29. The cell of any one of claims 23-28, wherein said cell is a hybridoma.

30. A method of generating the cell of claim 29, said method comprising the steps of:
(a) contacting lymphocytes with a heteromyeloma cell line under conditions that result in the fusion of a lymphocyte with a heteromyeloma cell, said fusion resulting in a hybridoma,
(b) determining whether said hybridoma produces a polypeptide that inhibits proliferation in a neoplastic cell to which it binds, but does not inhibit proliferation in a non-neoplastic cell and
(c) determining whether said hybridoma produces a polypeptide that specifically binds to BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU-NH91 (DSMZ Accession No. ACC 393) cells and not to non-neoplastic cells.

31. A method of generating the cell of claim 29, said method comprising the steps of:
(a) contacting lymphocytes with a heteromyeloma cell line under conditions that result in the fusion of a lymphocyte with a heteromyeloma cell, said fusion resulting in a hybridoma,
(b) determining whether said hybridoma produces a polypeptide that induces intracellular accumulation of lipids in a neoplastic cell to which it binds, but does not induce intracellular accumulation of lipids in a non-neoplastic cell and
(c) determining whether said hybridoma produces a polypeptide that specifically binds to BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F

to which it binds, but does not induce intracellular accumulation of lipids in a non-neoplastic cell and

(c) determining whether said hybridoma produces a polypeptide that specifically binds to BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU-NH91 (DSMZ Accession No. ACC 393) cells and not to non-neoplastic cells.

32. A method of generating the cell of claim 29, said method comprising the steps of:

(a) contacting lymphocytes with a heteromyeloma cell line under conditions that result in the fusion of a lymphocyte with a heteromyeloma cell, said fusion resulting in a hybridoma,

(b) determining whether said hybridoma produces a polypeptide that induces apoptosis of a neoplastic cell to which it binds, but does not induce apoptosis of a non-neoplastic cell, and

(c) determining whether said hybridoma produces a polypeptide that specifically binds to BXPC-3 (ATCC Accession No. CRL-1687), 23132/87 (DSMZ Accession No. ACC 201), COLO-206F (DSMZ Accession No. ACC 21), COLO-699 (DSMZ Accession No. ACC 196), and LOU-NH91 (DSMZ Accession No. ACC 393) cells and not to non-neoplastic cells.

33. Use of the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a method of diagnosing a neoplasm in a mammal, said method comprising the steps of:

(a) contacting a cell or tissue sample of said mammal with the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 and

(b) detecting whether said purified polypeptide binds to said cell or tissue sample, wherein binding of said purified polypeptide to said cell or tissue sample is indicative of said mammal having a neoplasm.

34. The use of claim 33, wherein said mammal is a human.

35. The use of claim 33, wherein said neoplasm is a adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus cell.

36. The use of claim 33, wherein said polypeptide is an antibody.

37. The use of claim 33, wherein said polypeptide is conjugated to a detectable agent selected from the group consisting of a radionuclide, a fluorescent marker, an enzyme, a cytotoxin, a cytokine, and a growth inhibitor.

38. The use of claim 33, wherein said polypeptide is conjugated to a protein purification tag.

39. The use of claim 38, wherein said protein purification tag is cleavable.

40. Use of the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19

or 20 in a method of treating a proliferative disorder in a mammal, said method comprising the step of contacting a cell or tissue sample with the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 18, 19, 20 or 21, wherein binding of said purified polypeptide to said cell or tissue sample results in a reduction in proliferation of said cell or of a cell in said tissue sample.

41. The use of claim 40, wherein said mammal is a human.

42. The use of claim 40, wherein said proliferative disorder is a adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus.

43. The use of claim 40, wherein said polypeptide is an antibody.

44. The use of claim 40, wherein said polypeptide is conjugated to a detectable agent selected from the group consisting of a radionuclide, a fluorescent marker, an enzyme, a cytotoxin, a cytokine, and a growth inhibitor.

45. The use of claim 44, wherein said detectable agent is capable of inhibiting cell proliferation of said cell or tissue sample.

46. The use of claim 44, wherein said polypeptide is conjugated to a protein purification tag.

47. The use of claim 46, wherein said protein purification tag is cleavable.

48. Use of the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a method of treating a proliferative disorder in a mammal, said method comprising the step of contacting a cell or tissue sample with the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 18, 19, 20 or 21, wherein binding of said purified polypeptide to said cell or tissue sample results in the intracellular accumulation of lipids of said cell or of a cell in said tissue sample.

49. The use of claim 48, wherein said mammal is a human.

50. The use of claim 48, wherein said proliferative disorder is a adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary, and adenocarcinoma of the uterus.

51. The use of claim 48, wherein said polypeptide is an antibody.

52. The use of claim 48, wherein said polypeptide is conjugated to a detectable agent selected from the group consisting of a radionuclide, a fluorescent marker, an enzyme, a cytotoxin, a cytokine, and a growth inhibitor.

53. The use of claim 52, wherein said detectable agent is capable of inhibiting cell proliferation of said cell or tissue sample.

54. The use of claim 52, wherein said polypeptide is conjugated to a protein purification tag.

55. The use of claim 54, wherein said protein purification tag is cleavable.

56. Use of the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a method of treating a proliferative disorder in a mammal, said method comprising the step of contacting a cell or tissue sample with the purified polypeptide of claim 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 wherein binding of said purified polypeptide to said cell or tissue sample results in the induction of apoptosis of said cell or tissue sample.

57. The use of claim 56, wherein said mammal is a human.

58. The use of claim 56, wherein said proliferative disorder is a adenocarcinoma of the lung, squamous cell lung carcinoma, intestinal type gastric carcinoma, diffuse type gastric carcinoma, adenocarcinoma of the colon, adenocarcinoma of the prostate, squamous cell carcinoma of the esophagus, adenocarcinoma of the esophagus, lobular carcinoma of the breast, ductal carcinoma of the breast, adenocarcinoma of the pancreas, adenocarcinoma of the ovary and adenocarcinoma of the uterus

59. The use of claim 56, wherein said polypeptide is an antibody.

60. The use of claim 56, wherein said polypeptide is conjugated to a detectable agent selected from the group consisting of a radionuclide, a fluorescent marker, an enzyme, a cytotoxin, a cytokine, and a growth inhibitor.

61. The use of claim 60, wherein said detectable agent is capable of inducing apoptosis of said cell or tissue sample.

62. The use of claim 60, wherein said polypeptide is conjugated to a protein purification tag.

63. The use of claim 62, wherein said protein purification tag is cleavable.

64. Purified polypeptide of any one of claims 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a pharmaceutically acceptable carrier for the production of a medicament that inhibits cell proliferation.

65. Purified polypeptide of any one of claims 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a pharmaceutically acceptable carrier for the production of a medicament that induces the intracellular accumulation of lipids.

66. Purified polypeptide of any one of claims 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a pharmaceutically acceptable carrier for the production of a medicament that induces apoptosis.

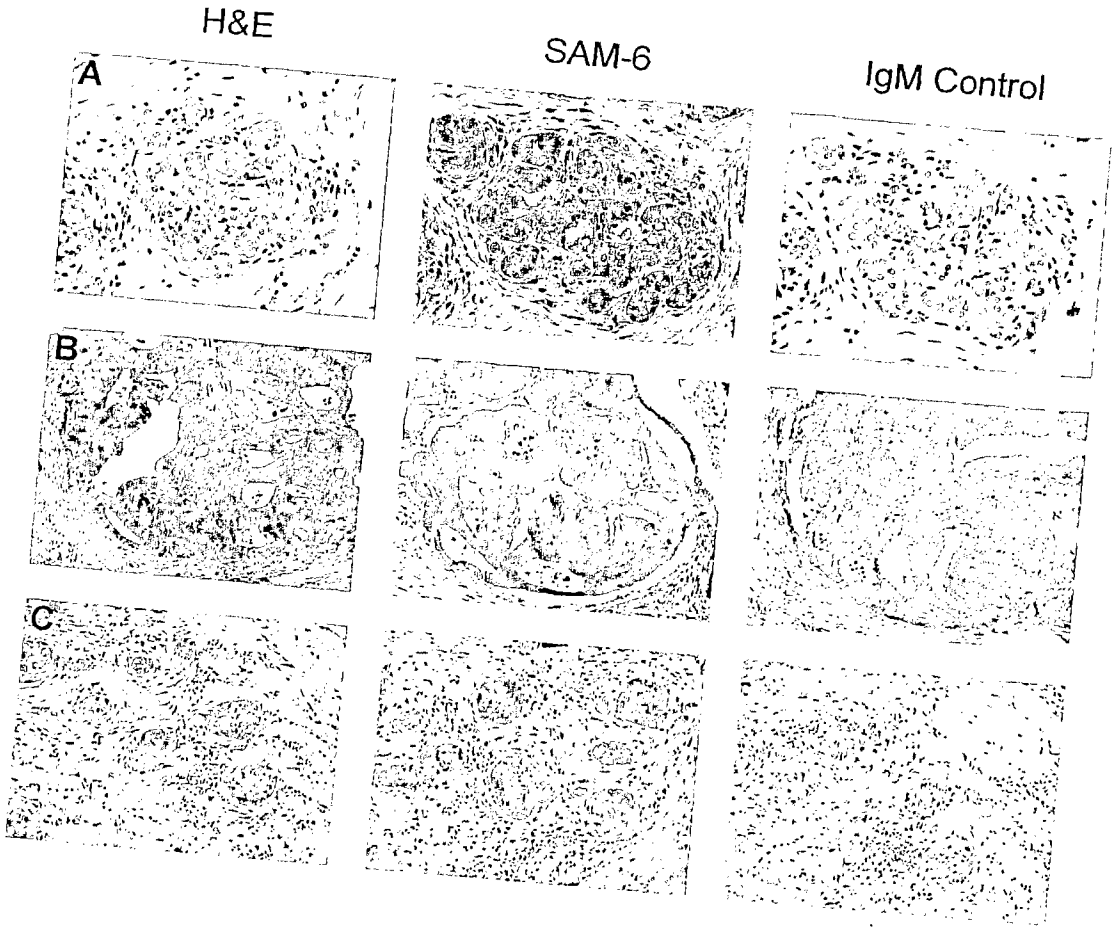
67. Purified polypeptide of any one of claims 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20 in a pharmaceutically acceptable carrier for the production of a medicament that inhibits cell proliferation and induces the intracellular accumulation of lipids and induces apoptosis.

68. A diagnostic agent comprising the purified polypeptide of any one of claims 1, 2, 3, 4, 5, 6, 17, 18, 19 or 20.

69. An isolated nucleic acid molecule comprising the sequence of SEQ ID NO:2 or 4.

70. A vector comprising the nucleic acid molecule of claim 69.

71. A cell comprising the vector of claim 70.



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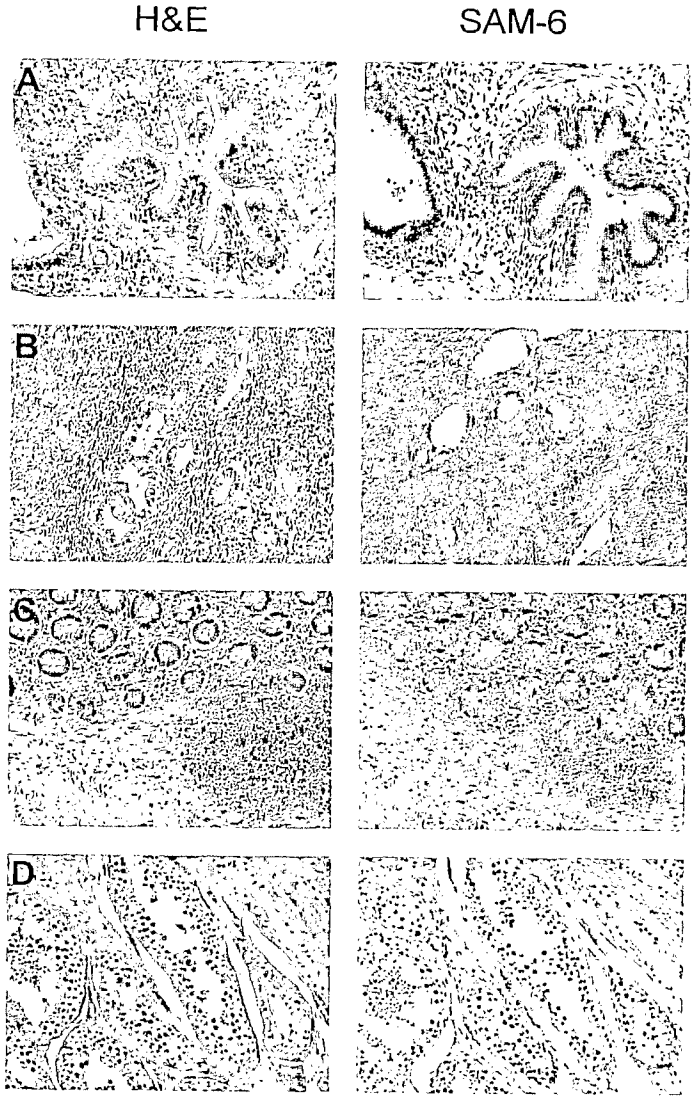

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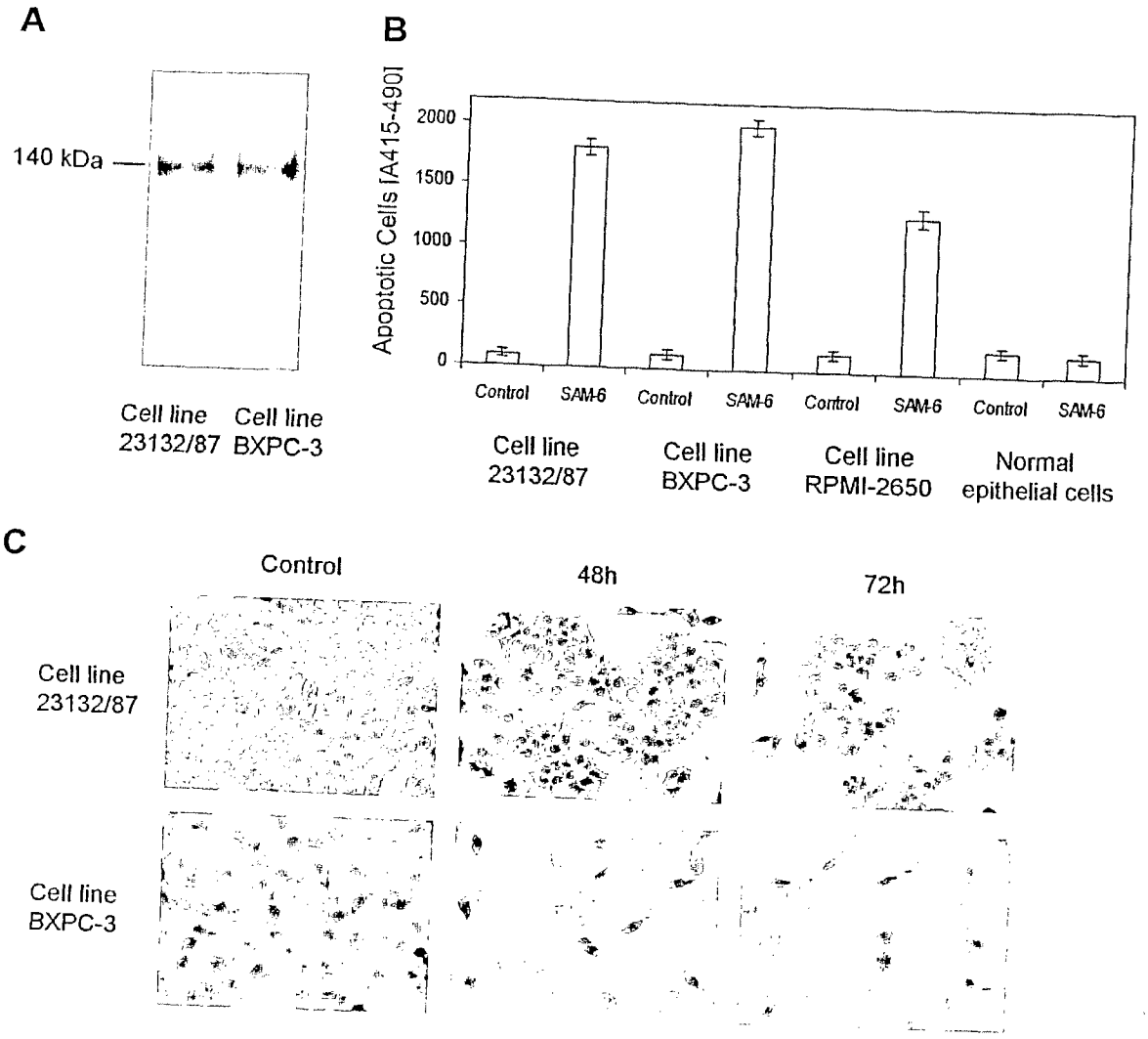
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Control
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Control
SAM-6
Control
SAM-6
Control
SAM-6
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Control
48h
72h
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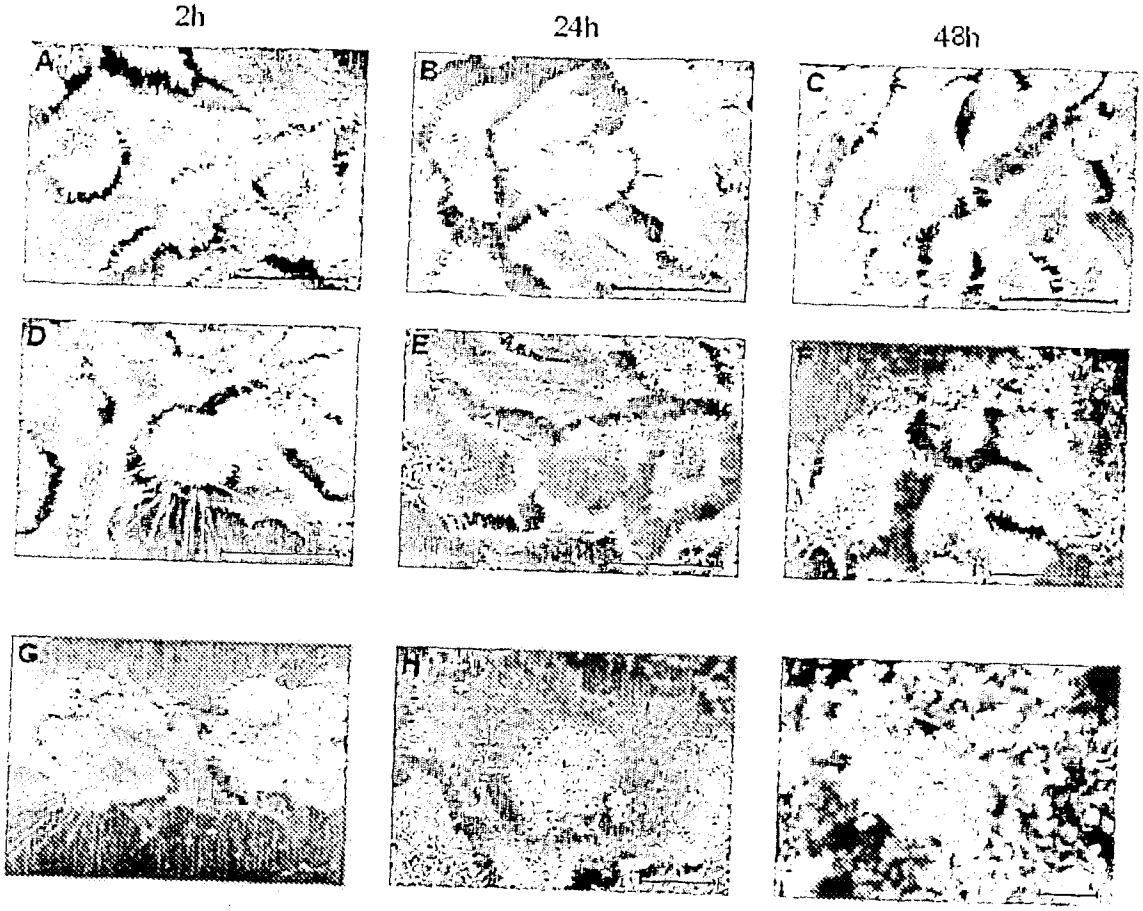
Cell line BXPC-3

Figure 3



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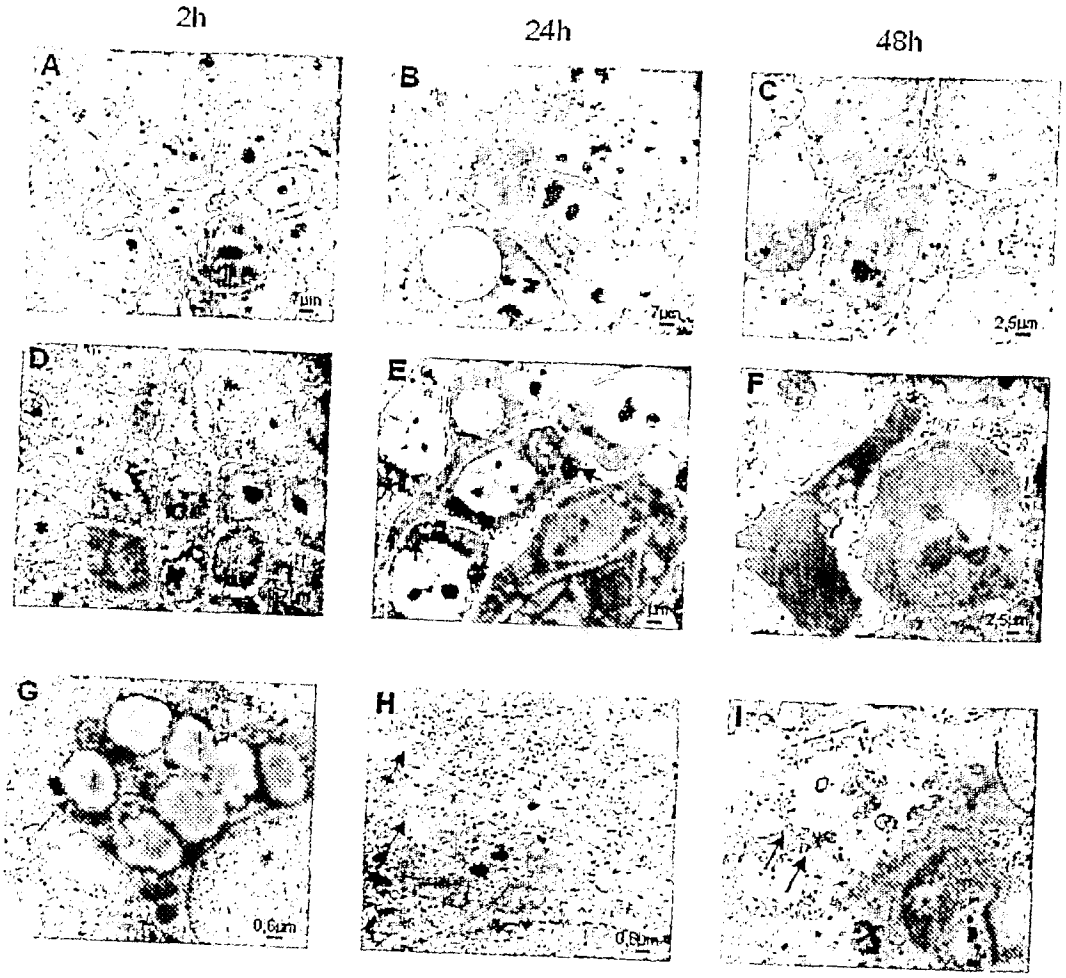

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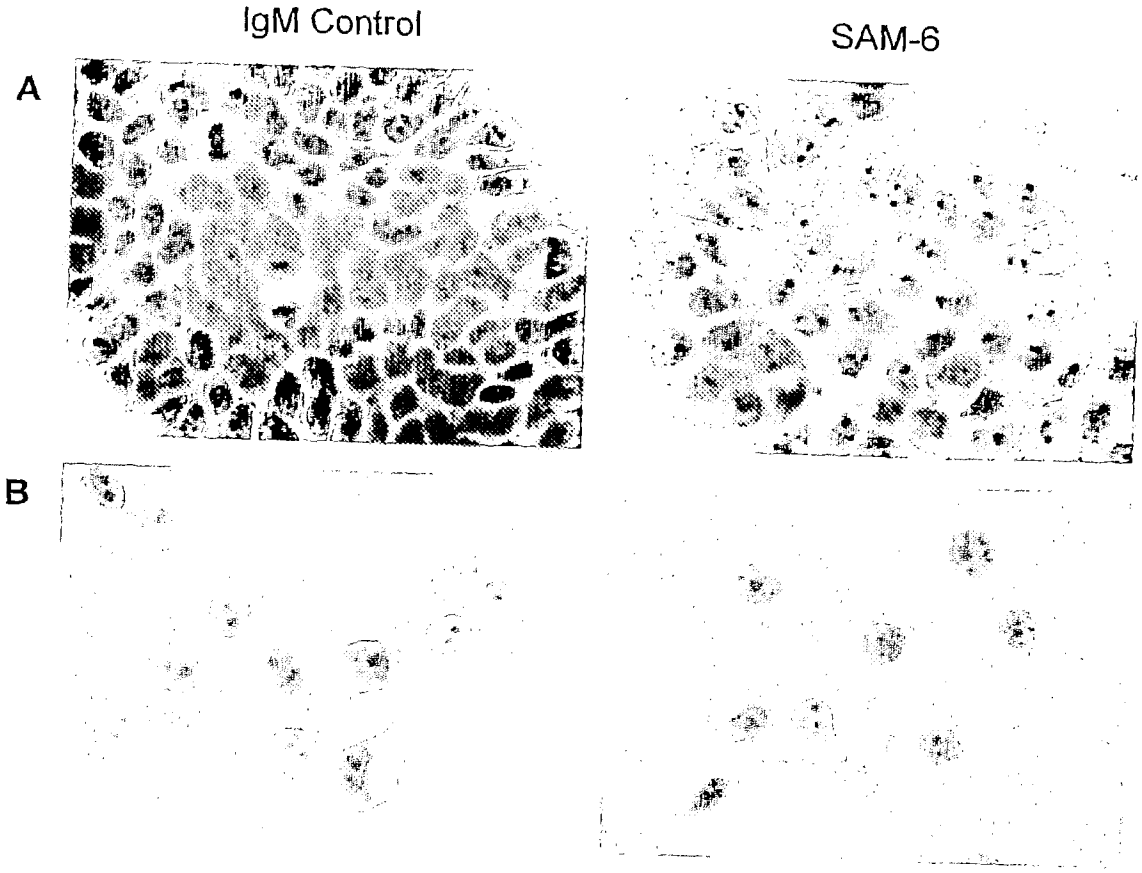

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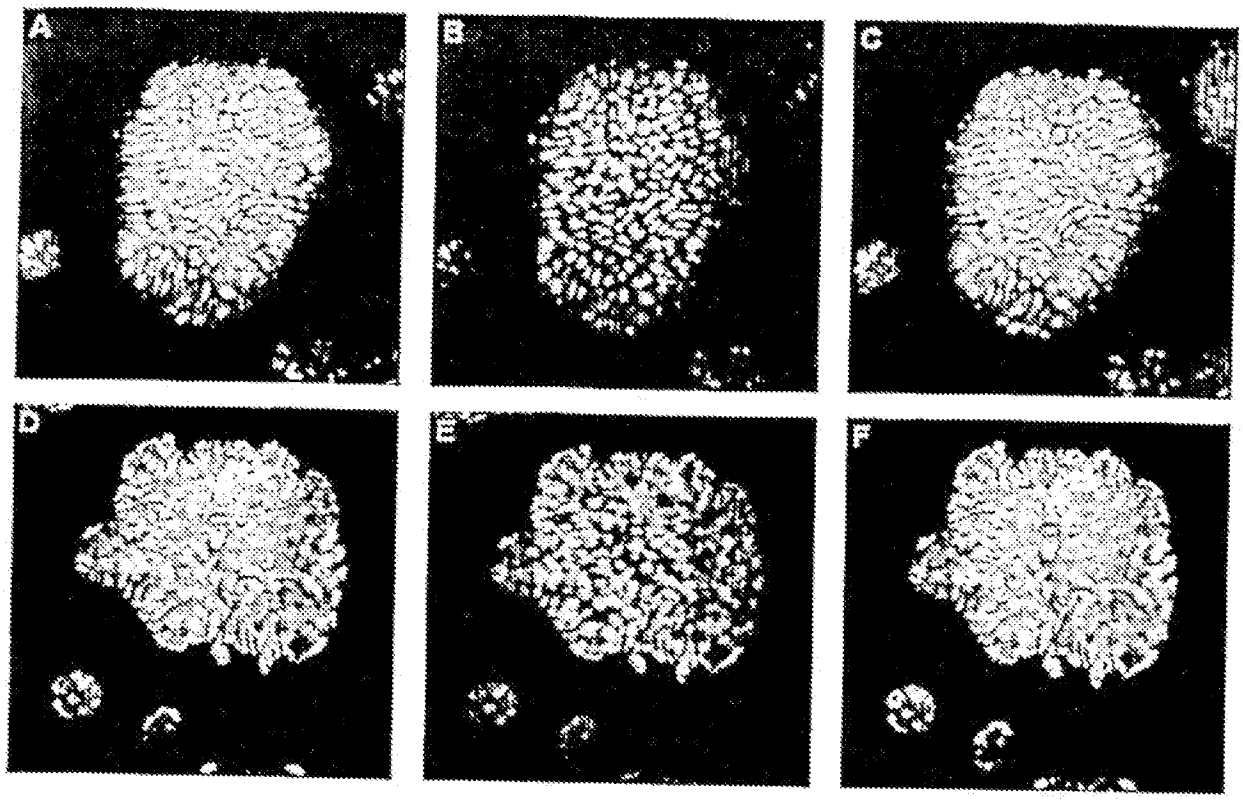

Figure 7

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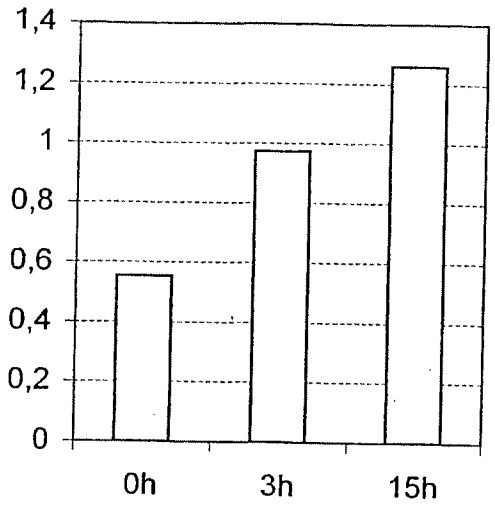
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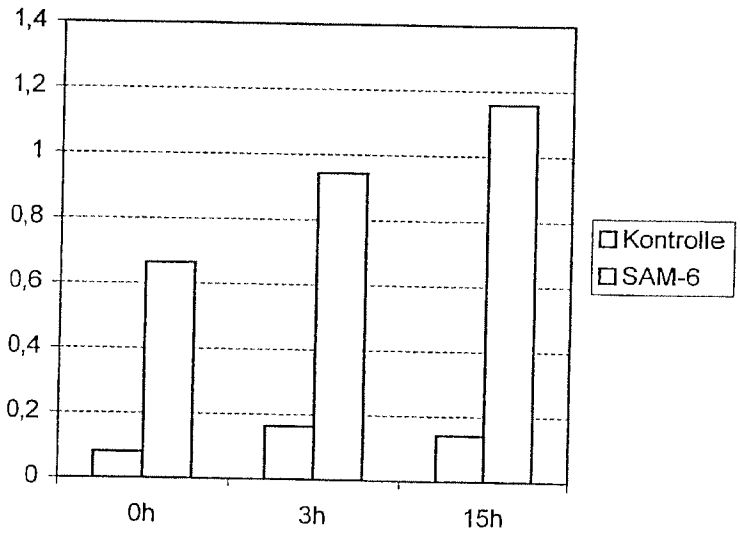
0,2
0
0h
3h
15h

B


1,4
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0,6
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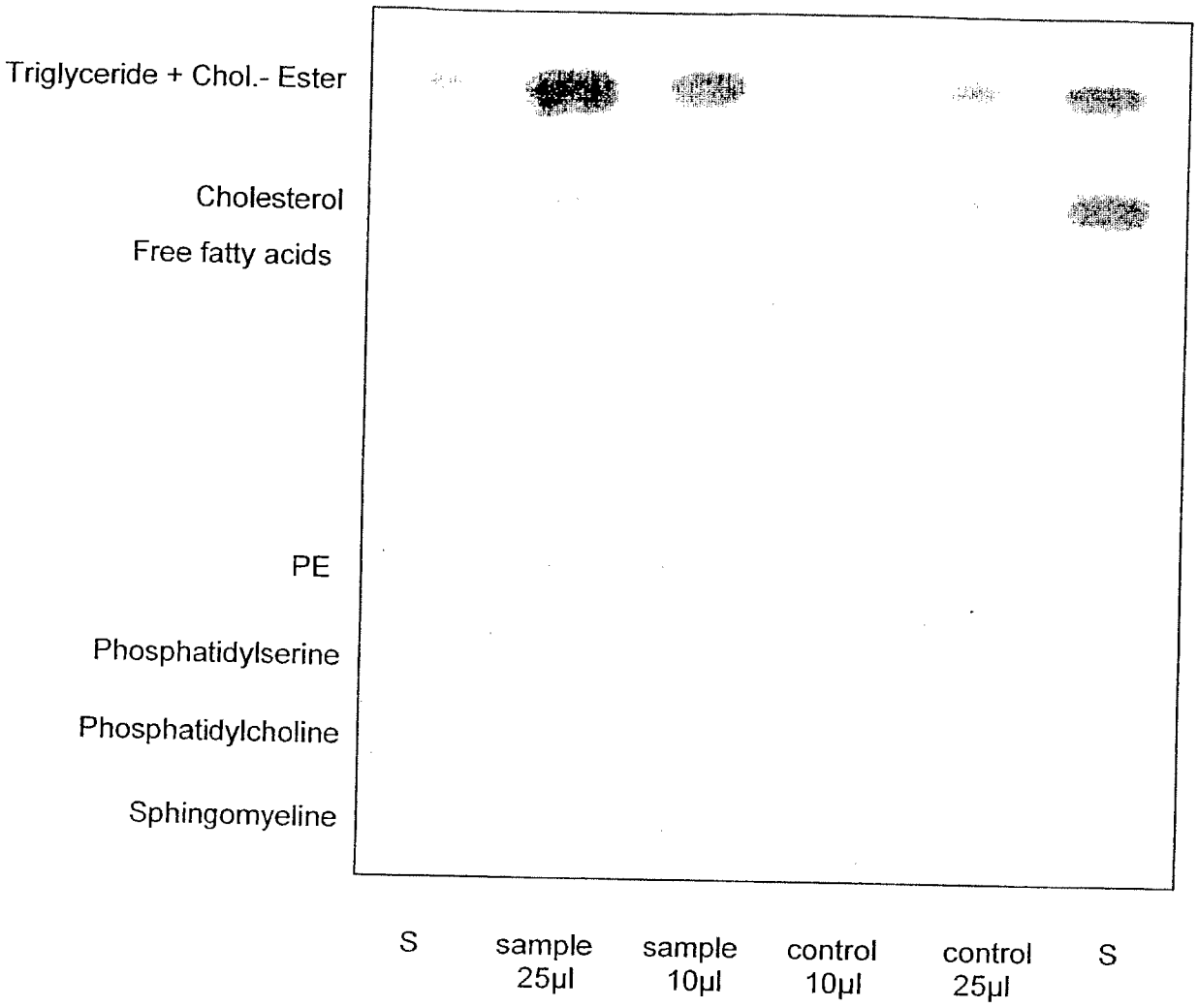
0,2
0
0h
3h
15h
Kontrolle
SAM-6

Figure 8

A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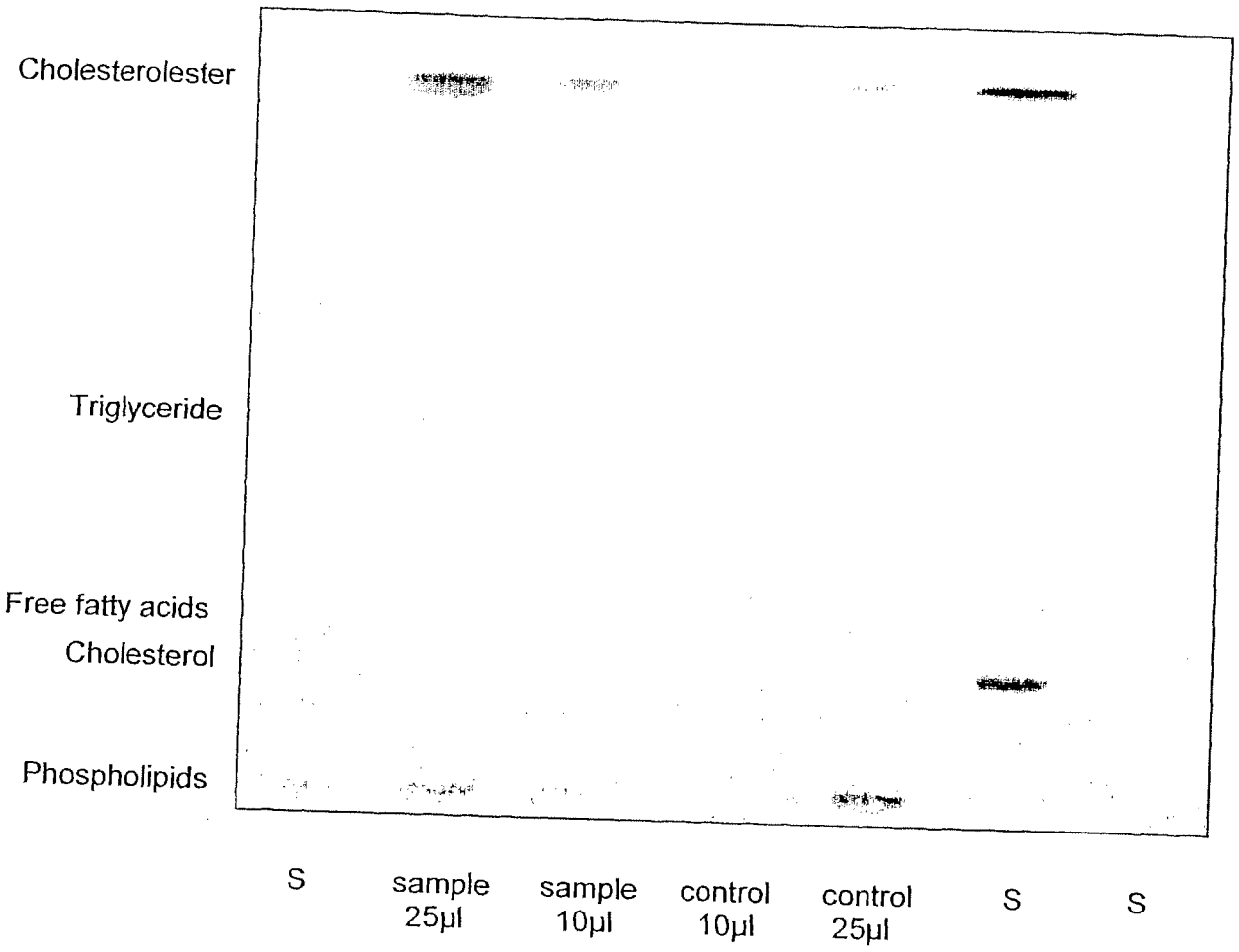
Cholesterol
Free fatty acids
PE
Phosphatidylserine
Phosphatidylcholine
Sphingomyeline
S
sample 25µl
sample 10µl
control 10µl
control 25µl
S

Figure 9a

B


Cholesterolester
Triglyceride
Free fatty acids
Cholesterol
Phospholipids
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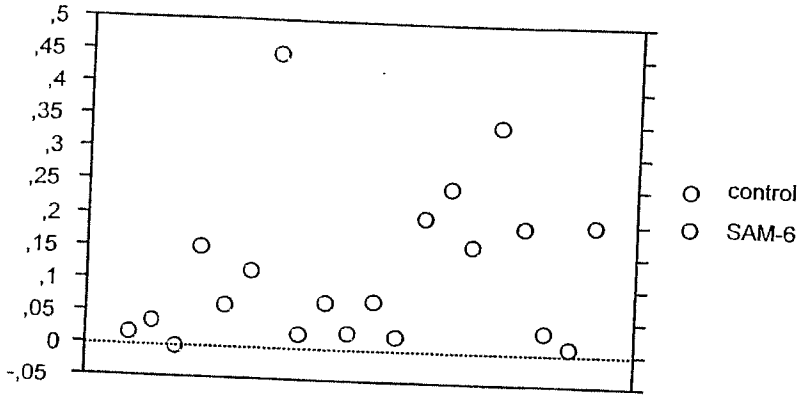
sample 10µl
control 10µl
control 25µl
S
S

Figure 9b

A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0
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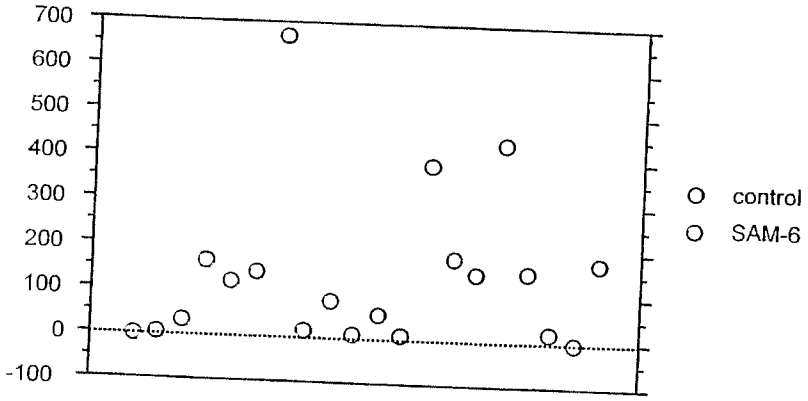
control
SAM-6

B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300
200
100
0
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control
SAM-6

Figure 10

Sequence listing

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<151> 2003-11-14

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        35                  40                  45

Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg
    50                  55                  60

Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
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                                                  CDR1
cag aca gcc agc atc acc tgc tct gga gat aaa ttg ggg gat aaa          90
Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp Lys
            20                  25                  30

tat gct tgc tgg tat cag cag aag cca ggc cag tcc cct gtg ctg         135
Tyr Ala Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
        35                  40                  45

                CDR2
gtc atc tat caa gat agc aag cgg ccc tca ggg atc cct gag cga         180
Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg
    50                  55                  60

ttc tct ggc tcc aac tct ggg aac aca gcc act ctg acc atc agc         225
Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
65                  70                  75

ggg acc cag gct atg gat gag gct gac tat tac tgt cag gcg tgg         270
Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp
            80                  85                  90

    CDR3
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        95
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            20                  25                  30

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        35                  40                  45

Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr
    50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
65                  70                  75

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            80                  85                  90

Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Leu Ala Val Ala Gly
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Lys Thr Phe Asp Tyr
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 1               5                  10                  15

agg tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc agt          90
Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
            20                  25                  30
      CDR1
     ----------
agc tat gct atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg         135
Ser Tyr Ala Met His Trp Val Arg Glu Ala Pro Gly Lys Gly Leu
            35                  40                  45
                                CDR2
                    ------------------------------------
gag tgg gtg gca gtt ata tca tat gat gga agc aat aaa tac tac         180
Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr
            50                  55                  60

---------------
gca gac tcc gtg aag ggc cga ttc acc atc tcc aga gac aat tcc         225
Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
            65                  70                  75

aag aac acg ctg tat ctg caa atg aac agc ctg aga gct gag gac         270
Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
            80                  85                  90
                                CDR3
                    ------------------------------------
acg gct gtg tat tac tgt gcg aga gat cgg tta gca gtg gct ggt         315
Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Leu Ala Val Ala Gly
            95                  100                 105

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aaa act ttt gac tac
Lys Thr Phe Asp Tyr
            110
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/012970

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/30 C12N5/12 C07K7/06 G01N33/574 G01N33/577
A61K47/48 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 03/076472 A (MUELLER-HERMELINK HANS KONRAD ;ONCOMAB GMBH (DE); VOLLMERS HEINZ P) 18 September 2003 (2003-09-18) page 2, line 6 - line 25 page 18, line 21 - line 24	1-71
X	VOLLMERS H PETER ET AL: "Adjuvant therapy for gastric adenocarcinoma with the apoptosis-inducing human monoclonal antibody SC-1: First clinical and histopathological results" ONCOLOGY REPORTS, vol. 5, no. 3, May 1998 (1998-05), pages 549-552, XP009015315 ISSN: 1021-335X the whole document	1-71

-/--

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 April 2005	02/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Le Flao, K

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/53051 A (GENSET SA ;DUCLERT AYMERIC (FR); DUMAS MILNE EDWARDS JEAN BAPTI (F) 21 October 1999 (1999-10-21) claim 3	1-22
X	WO 02/12502 A (CENTOCOR INC) 14 February 2002 (2002-02-14) figure SEQ	1-22
X	WO 00/12562 A (GENENTECH INC) 9 March 2000 (2000-03-09) figure 2	22
X	US 5 639 863 A (DAN MICHAEL D) 17 June 1997 (1997-06-17) figure SEQ	22
X	WO 02/084277 A (ABMAXIS INC ;LUO PEIZHI (US)) 24 October 2002 (2002-10-24) figure 8	22
A	HENSEL FRANK ET AL: "Regulation of the new coexpressed CD55 (decay-accelerating factor) receptor on stomach carcinoma cells involved in antibody SC-1-induced apoptosis" LABORATORY INVESTIGATION, vol. 81, no. 11, November 2001 (2001-11), pages 1553-1563, XP008029819 ISSN: 0023-6837 the whole document	1-71
P,X	POHLE TINA ET AL: "Lipoptosis: Tumor-specific cell death by antibody-induced intracellular lipid accumulation" CANCER RESEARCH, vol. 64, no. 11, 1 June 2004 (2004-06-01), pages 3900-3906, XP002324184 ISSN: 0008-5472 the whole document	1-71

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/012970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03076472 A	18-09-2003	DE 10210427 A1	09-10-2003
		AU 2003214537 A1	22-09-2003
		CA 2478116 A1	18-09-2003
		EP 1485415 A2	15-12-2004
		WO 03076472 A2	18-09-2003
WO 9953051 A	21-10-1999	AU 764571 B2	21-08-2003
		AU 3050199 A	01-11-1999
		CA 2319089 A1	21-10-1999
		EP 1068312 A2	17-01-2001
		WO 9953051 A2	21-10-1999
		JP 2002511259 T	16-04-2002
		US 6822072 B1	23-11-2004
WO 0212502 A	14-02-2002	US 2003049725 A1	13-03-2003
		AU 7922701 A	18-02-2002
		BR 0113110 A	16-09-2003
		CA 2419205 A1	14-02-2002
		CN 1468308 A	14-01-2004
		EP 1309691 A2	14-05-2003
		HU 0302376 A2	28-10-2003
		JP 2004523209 T	05-08-2004
		MX PA03001231 A	15-10-2003
		NO 20030620 A	31-03-2003
		NZ 524147 A	25-02-2005
		PL 360438 A1	06-09-2004
		WO 0212502 A2	14-02-2002
		US 2004120952 A1	24-06-2004
		ZA 200301856 A	21-06-2004
WO 0012562 A	09-03-2000	AT 217889 T	15-06-2002
		AU 766551 B2	16-10-2003
		AU 5692399 A	21-03-2000
		BR 9913435 A	25-09-2001
		CA 2341276 A1	09-03-2000
		CN 1317015 A	10-10-2001
		DE 69901569 D1	27-06-2002
		DE 69901569 T2	19-12-2002
		DK 1107996 T3	16-09-2002
		EP 1107996 A1	20-06-2001
		ES 2177316 T3	01-12-2002
		JP 2002523081 T	30-07-2002
		NZ 509430 A	26-04-2002
		PT 1107996 T	31-10-2002
		WO 0012562 A1	09-03-2000
		US 6624295 B1	23-09-2003
		ZA 200100681 A	24-01-2002
US 5639863 A	17-06-1997	AT 205532 T	15-09-2001
		AU 686394 B2	05-02-1998
		AU 2709295 A	15-01-1996
		CA 2192079 A1	28-12-1995
		WO 9535374 A1	28-12-1995
		CN 1151184 A ,C	04-06-1997
		DE 69522689 D1	18-10-2001
		DE 69522689 T2	08-08-2002
		EP 0766736 A1	09-04-1997
		JP 10501411 T	10-02-1998

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/012970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5639863 A		NO 965395 A	17-12-1996
		NZ 288157 A	29-09-1999
WO 02084277 A	24-10-2002	CA 2443862 A1	24-10-2002
		EP 1390741 A1	25-02-2004
		WO 02084277 A1	24-10-2002
		US 2003054407 A1	20-03-2003
		US 2002177170 A1	28-11-2002
		US 2003022240 A1	30-01-2003
		US 2004010376 A1	15-01-2004
		US 2004133357 A1	08-07-2004